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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Schreiber *et al.*	Examiner:	Solola, Taofiq A.
Serial No.:	10/649,532	Art Unit:	1639
Filing Date:	August 27, 2003		
Title:	DIHYDROPYRANCARBOXAMIDES AND USES THEREOF		

Mail Stop: AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 C.F.R. 1.131

I, Robert A. Stavenger, Ph.D., declare as follows:

1. I am an inventor of the subject matter disclosed and claimed in United States Patent Application Serial No. 10/649,532 ('532 application) filed August 27, 2003, and entitled " DIHYDROPYRANCARBOXAMIDES AND USES THEREOF". This application claims priority to United States provisional patent application Serial No. 60/406,140, filed on August 27, 2002.

2. This Declaration is presented for the purpose of removing from consideration by the Examiner the following two papers:

(i) Clemons *et al.* "A one-bead, one-stock solution approach to chemical genetics: part 2", *Chem. Biol.* 8:1183-1195, 2001 (hereinafter, "Clemons"). As indicated on the front page of the paper, the article first published online on November 7, 2001. Thus, the paper first became available to the public on November 7, 2001.

(ii) Blackwell *et al.* "Decoding Products of Diversity Pathways from Stock Solutions Derived from Single Polymeric Macrobeads", *Angew. Chem. Int. Ed.* 40(18):3421-3425, 2001 (hereinafter, "Blackwell"). The paper first became available to the public on September 14, 2001.

Therefore, both the Clemons and Blackwell papers became available to the public less than one year prior to the filing of the provisional application to which the present application claims priority.

The present Declaration is presented in accordance with In re Stompel, 113 U.S.P.Q. 77 (CCPA 1957) and establishes conception and reduction to practice of the invention in this country before September 14, 2001.

3. While the publication date of the edition of Angewandte Chemie International Edition in which Blackwell appeared was September 17, 2001, the article was first published online on September 14, 2001 as indicated in the print out of the Journal's web page (Exhibit 1, page 5).

4. The inventors of the claimed subject matter of United States Patent Application Serial No. 10/649,532 are Stuart L. Schreiber, Robert A. Stavenger, Timothy J. Mitchison, and Zoltan Maliga.

5. On a date before September 14, 2001, Stuart L. Schreiber, Timothy J. Mitchison, and Zoltan Maliga and I conceived and reduced to practice our invention of dihydropyrancarboxamide compounds and uses thereof.

6. Exhibit 2 is a copy of several pages from my laboratory notebook, with dates blacked out. Exhibit 2 provides evidence of conception and actual reduction to practice of the claimed invention prior to September 14, 2001. In particular, pages 17-20, 22-24 and 26-29 include a description of a synthesis of a library of dihydropyrancarboxamide compounds, using vinyl ether, unsaturated ketoester and amine building blocks disclosed in the specification, as filed. For example, page 17 describes vinyl ether building blocks BB1-A through BB1-H depicted on page 61 of the specification. Page 20 describes unsaturated ketoester building blocks BB2-A through BB2-J depicted on page 62 of the specification. Page 26 describes amine building blocks BB3-A through BB3-Y depicted on page 66 of the specification. Finally, pages 31-34 include a description of the decoding process of the dihydropyrancarboxamide library. The notes were prepared in the United States of America.

7. The originals of these documents bear dates prior to September 14, 2001.

8. All statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patents issued thereon.

Robert A. Stavenger, Ph.D.

Aug 30, 2006
Date

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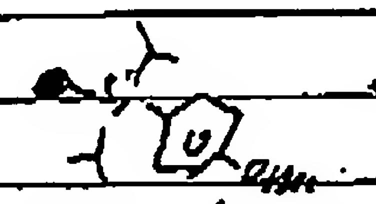
Making the library — Step 1 → loading.

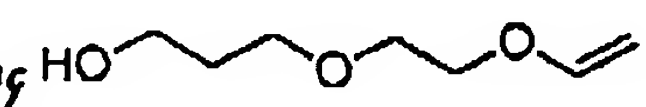
 + TfOH +  + ROH

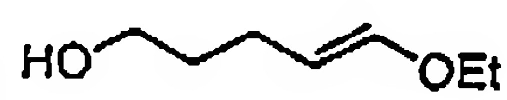
MW	143mg/g mX-1	150.07 (1.696)	107.16 (0.920)	see below
amount	262mg × 8 —	200μL	350μL	
mmol	0.375 × 8	2.25	3.0	0.75
eq	1.0	6.0	8.0	2.0

Resin (in PP10 columns) suspended in fresh 3% TMSCl/CH₂Cl₂ (v/v) (3mL) + allowed to stand for 30 min. Filtered (Ar pressure) + washed (4×3mL×2min CH₂Cl₂) + TfOH (as ~3% soln in CH₂Cl₂ ~8.6mL) added – resin turned orange immediately, eventually red. allowed to stand (agitated occasionally) for 25 min. Filtered + washed as above and left in 2mL CH₂Cl₂. Lutidine added + color discharged – allowed to stand for 15 min then vinyl ethers (as soln in 1mL CH₂Cl₂) added. Allowed to stand for 2.5h then washed 3×5mL×2min CH₂Cl₂ then 1×5mL 45min THF then 4×5mL×15min CH₂Cl₂. dried (first vac. to filter, then hi vac ~2h)

proceed to pg 18 — 78-79

A 87mg 
$C_6H_{12}O_2$
Mol. Wt.: 116.16

B 110mg 
$C_7H_{14}O_3$
Mol. Wt.: 146.18

C 98mg 
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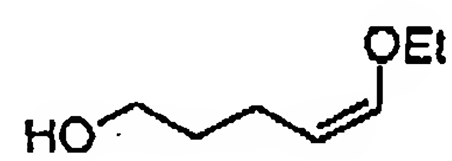
D 98mg 
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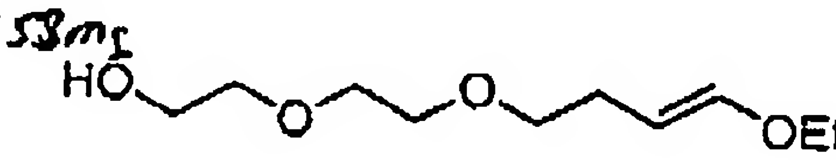
Mol. Wt.: 130.18

E 158mg 
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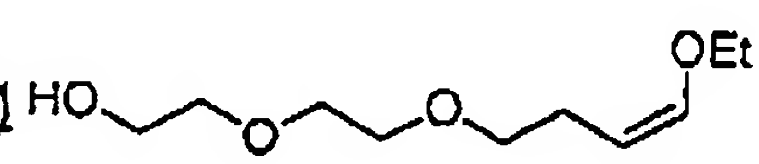
Mol. Wt.: 204.26

F 153mg 
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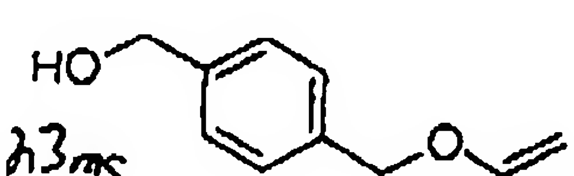
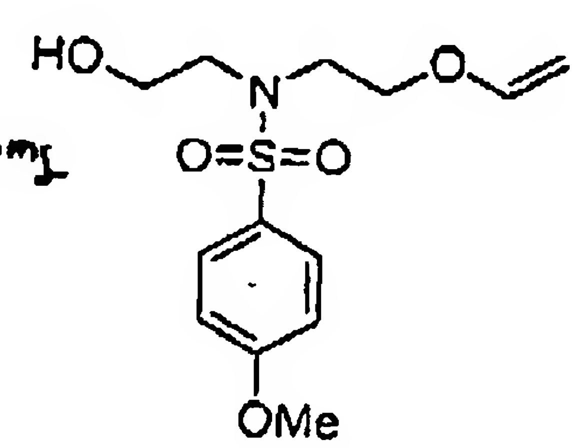
Mol. Wt.: 204.26

G 123mg 
$C_{10}H_{12}O_2$
Mol. Wt.: 164.20

H 226mg 
$C_{13}H_{19}NO_5S$
Mol. Wt.: 301.36

18

Making the Library - step 2 - 1st encoding

8 Resin pools from pp 17 A → H

Scheme →

resin pool	T_2B (C_4Cl_3)	T_4B (C_6Cl_3)	T_1A (C_3Cl_5)	T_2A (C_4Cl_5)
A	X			
B		X		
C			X	
D				X
E	X	X		
F	X		X	
G	X			X
H		X	X	

Procedure:

each batch of resin placed in dry 8mL vial.
tags added (~~16.8m~~ for 16.8mM conc TA b soln total conc ~~=~~ ie (in 4mL CH_4) is 6.72×10^{-5} moles/tag for one (1) tag steps (A, B, C, D) and 3.36×10^{-5} moles/tag for two (2) tag steps (E F G H). → see weights on next page 9 - note: no addition

The dry tag + resin was put under Ar + CH_2Cl_2 added to each vial (4mL) - shaken for 1 h @ rt. then catalyst sol'n. (4mL of 2.5mg/mL) added w/ shaking. shaken 4h then filtered and washed.

cat: ($Ph_3CCO_2)_4Rh_2$

2 x 15min x 5mL CH_2Cl_2 1 x 5mL x 5min THF, 1 x 5mL x 0h THF
2 x 5mL x 10min THF, 3 x 5mL x 15min CH_2Cl_2 - dried

(cont.)

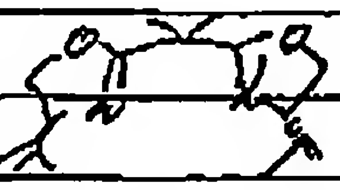
resin pool	T_2B (C_4Cl_3) mw 443.7	T_4B (C_6Cl_3) mw 471.75	T_1A (C_3Cl_5) mw 498.58	T_2A (C_4Cl_5) mw 512.61
A	29.7 mg	∅	∅	∅
B	∅	31.8 mg	∅	∅
C	∅	∅	33.5 mg	∅
D	∅	∅	∅	34.5 mg
E	14.9 mg	15.9 mg	∅	∅
F	14.9 mg	∅	16.7 mg	∅
G	14.9 mg	∅	∅	17.2 mg
H	∅	15.9 mg	16.7 mg	∅

Resin pooled + rotated in solvent 1×15 mL×30 min THF, 3×15 mL×30 min CH_2Cl_2

dried

→ 2.12 g resin after drying. divide into 20 equal portions → 106 mg each. Take these on to "cycloadd" step. see next page

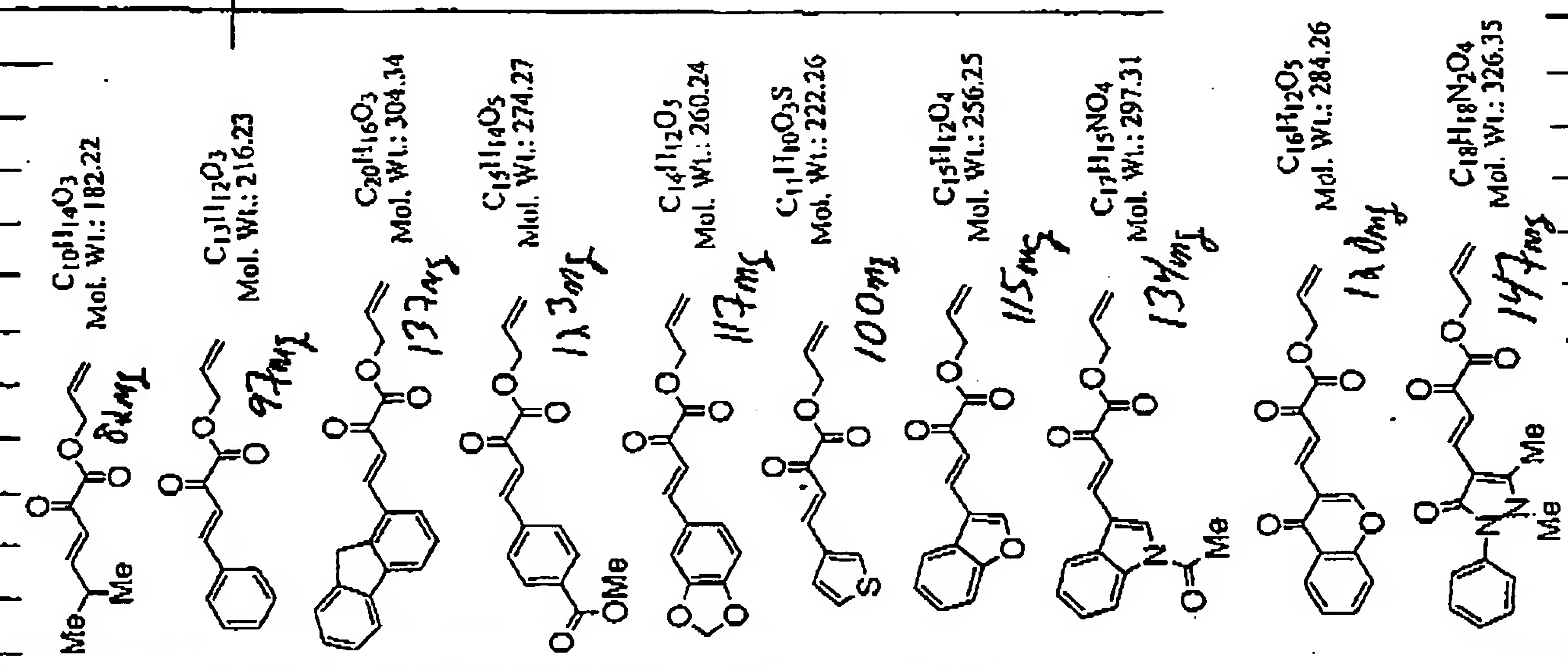
Making the library step 3:
Cycloaddition:

vinyl ether resin +  + Cu(OTf)$_2$ + 4Å MS
(S)-cat

stock soln of catalyst → 14.1mg ligand + 9.3mg Cu(OTf)$_2$
+ 50mg sieves in 12.8mL THF stirred @ rt for 1h
deep green color

Resin from 19 (20 vials) added to vials containing
dienes (see below) + 10mg sieves) then put under Ar
+ 800uL dry THF added, followed by 800uL catalyst
soln (20 mol %). Vials shaken for 20 h then
washed - 4×5mL ×30 min THF, 3×5mL ×15 min CH_2Cl_2
dried and moved to next step (pp 22-23)

each vial = 0.15 mmol of resin.
use 3 eq of diene - 0.45 mmol
eq



A B C D E F G H I J

22

Making the Library Step 4 - tagging 2

The 20 pools from pg 20-21 were treated as below -

Resin and tags (see next page for masses. - 16.8 mM Tag Soln in 1.6 mL CH_2Cl_2 is 2.688×10^{-5} mol/tag for 1 tag (20A-20E) 1.344×10^{-5} mole/tag for 2 tags (20F-21E) and 0.896×10^{-5} mole/tag for 3 tags (21F-21J). ϕ = no add^n.

Dry resin and tag in DnL dry vial under Ar. 1.6 mL CH_2Cl_2 added and shaken gently for 1 h. Then catalyst (1.6 mL of 2.5 mg/mL soln in CH_2Cl_2) added and vials shaken overnight.

Solvent filtered + washed 2 x 5 mL + 15 min CH_2Cl_2, 2 x 5 mL x 15 min THF, 1 x 5 mL x 6 h THF, 2 x 5 mL + 15 min THF, 7 x 5 mL + 15 min CH_2Cl_2

Resin pool	T3A (C5Cl5) mw 526.64	T4A (C6Cl5) mw 540.67	T5A (C7Cl5) mw 554.70	T6A (C8Cl5) mw 568.73	T7A (C9Cl5) mw 582.76
20A	X				
20B		X			
20C			X		
20D				X	
20E					X
20F	X	X			
20G	X		X		
20H	X			X	
20I	X				X
20J		X	X		
21A		X		X	
21B		X			X
21C			X	X	
21D			X		X
21E				X	X
21F	X	X	X		
21G	X	X		X	
21H	X	X			X
21I	X		X	X	
21J	X		X		X

(cont)

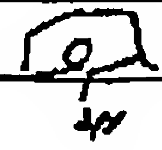
Resin pool	T3A (C5Cl5) mw 526.64	T4A (C6Cl5) mw 540.67	T5A (C7Cl5) mw 554.70	T6A (C8Cl5) mw 568.73	T7A (C9Cl5) mw 582.76
20A	14.2mg	ø	ø	ø	ø
20B	ø	14.5mg	ø	ø	ø
20C	ø	ø	14.9mg	ø	ø
20D	ø	ø	ø	15.3mg	ø
20E	ø	ø	ø	ø	15.7mg
20F	7.1mg	7.3mg	ø	ø	ø
20G	7.1mg	ø	7.5mg	ø	ø
20H	7.1mg	ø	ø	7.6mg	ø
20I	7.1mg	ø	ø	ø	7.9mg
20J	ø	7.3mg	7.5mg	ø	ø
21A	ø	7.3mg	ø	7.6mg	ø
21B	ø	7.3mg	ø	ø	7.9mg
21C	ø	ø	7.5mg	7.6mg	ø
21D	ø	ø	7.5mg	ø	7.9mg
21E	ø	ø	ø	7.6mg	7.9mg
21F	4.7mg	4.8mg	5.0mg	ø	ø
21G	4.7mg	4.8mg	ø	5.1mg	ø
21H	4.7mg	4.8mg	ø	ø	5.2mg
21I	4.7mg	ø	5.0mg	5.1mg	ø
21J	4.7mg	ø	5.0mg	ø	5.2mg

→ The resin vials (20A-J) - (21A-J) were pooled to give 20 pool and 21 pool (ie two enantiomeric pools). Mixed by washed in sonicat 2 × 15mL × 30 min. THF 3 × 15mL × 15 min CH_2Cl_2 then each pool dried to give

pool 20 → 1.4238g → split out 1/29 → 49.1mg
pool 21 → 1.4470g split out 1/29 49.9mg

taken to next step (pg 24)

Making the library step 5 - deallylation!

resin + $(Ph_3P)_4Pd$,  CO_2H —THF→

	resin	$(Ph_3P)_4Pd$	acid
mw		1155.8	154.19
amount		1.73 g	1.62 g
mmol	1.5	1.5	10.5
eq	1.0	1.0	10

Both resin pools treated as below.

Pd-cat dissolved in 26 mL THF, resin added followed by thiosalicylic acid → deep red mixture shaken for 12h.

Filtered and washed 4×15mL×1h THF, 2×15mL×15min DMF, 1×15mL×15min THF, 1×15mL×15min DMF, 4×15mL×15min CH_2Cl_2 then dried.

from 20 pool → 1.336g

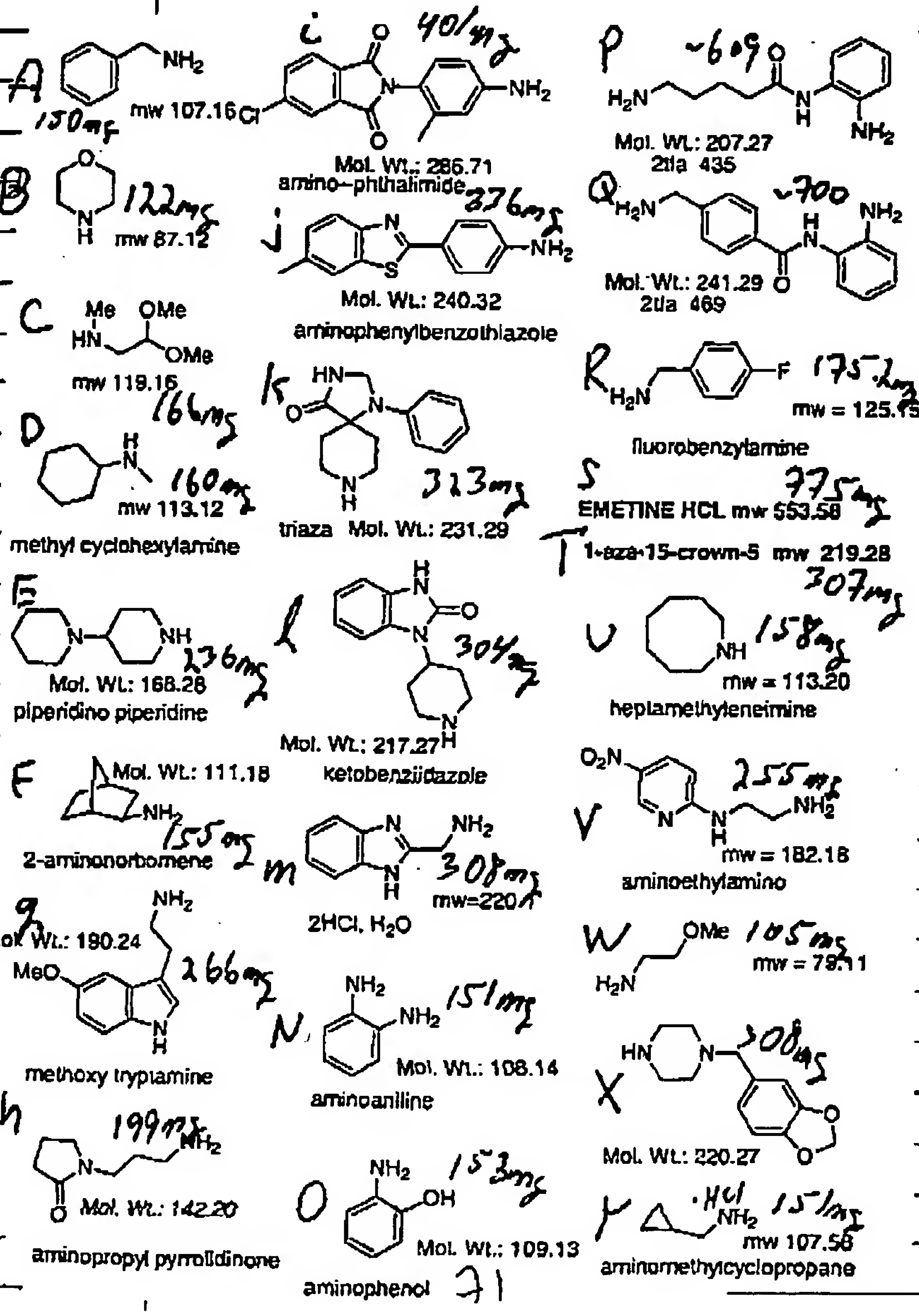
from 21 pool → 1.356g

Each pool then split into 26 equal portions
ie 20 pool → 51.4mg
21 pool → 52.2mg
and proceeded to next step
(pp 26-27)

Making the Library Step 6: amide formation

acids + amines + PyBOP + iPr$_2$NEt ⟶

mw		(var)	520.3	~~129.~~ 129.25 (0.742)
amount			290 mg	98 μL
mmol	~0.056	0.56		
eq	1.0		10	10



Stock solns of amines made w/ 1.5 equiv (1.4 mmols) each amine in 1.25 ml DMF. 500 μL (0.56 mmol) will then be added to each rxn - see next page.

26 → via resin from "20 pool"

27 → via resin from "21 pool"

To each vial of resin + stock soln of CH_2Cl_2/iPr$_2$EtOp was added (1.5 mL CH_2Cl_2 ~ 250 mg iPr$_2$EtOp) Then ~500 uL of DMF/amine stock solns (on page 26) added to appropriate vials. - some were not homogenous - added as slurry. Then iPrNEt (100 uL) added to every vial, w/ extra equiv if the amine was added as a salt (m, p, q, y)
Shaken overnight (12h)

Filtered and washed 2 x 1mL x 30 min CH_2Cl_2, 2 x 1mL x 30 min DMF, 2 x 30 min x 1mL THF 3 x 1mL x 30 min CH_2Cl_2. dried under high vacuum and kept separated in tubes.

28

LCMS Library

Resin pool	LCMS sample		Resin pool	LCMS sample
26a	1, 2		27a	51, 52
26b	3, 4		27b	53, 54
26c	5, 6		27c	55, 56
26d	7, 8		27d	57, 58
26e	9, 10		27e	59, 60
26f	11, 12		27f	61, 62
26g	13, 14		27g	63, 64
26h	15, 16		27h	65, 66
26i	17, 18		27i	67, 68
26j	19, 20		27j	69, 70
26k	21, 22		27k	71, 72
26l	23, 24		27l	73, 74
26m	25, 26		27m	75, 76
26n	27, 28		27n	77, 78
26o	29, 30		27o	79, 80
26p	31, 32		27p	81, 82
26q	33, 34		27q	83, 84
26r	35, 36		27r	85, 86
26s	37, 38		27s	87, 88
26t	39, 40		27t	89, 90
26u	41, 42		27u	91, 92
26v	43, 44		27v	93, 94
26w	45, 46		27w	95, 96
26x	47, 48		27x	97, 98
26y	49, 50		27y	99, 100
20 cycloaddition	101, 102		21 cycloaddition	103, 104
20 pool (acid)	105, 106		21 pool (acid)	107, 108

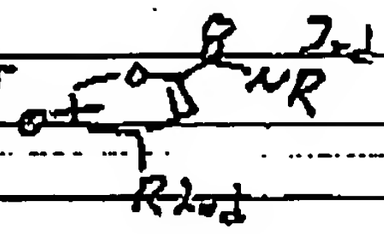
single beads in 700 µL eppendorf tubes, treated w/ 12.5 µL 85/10/5 THF/pyr/HF·pyr for 1.5 h, then treated w/ 12.5 mL TMSOMe for 30 min. evaporated the solvent, added 30 µL CH2Cl2 and transferred to autosampler vial.

transferred solns to 384 plate

Dimer cmpd cleavage:

Resin pool	mass	# of beads (counted)
RAS-L-292a	58.5mg	339
RAS-L-292c	47.2mg	212
RAS-L-294a	48.9mg	304
RAS-L-294c	37.9mg	250
RAS-L-297a	38.3mg	236
RAS-L-297c	47.3mg	260

LCMS Data: Upstream ppt D.



is agar

Area	Sample #	mass (MH+)	structure (L, M, S)	purity
Area A 107	1	571.7	hf	79%
	2	539.8	gj	
	51	487.8	gd	
	52	417.9	bf	
B 87	3	552.7	bf	
	4	425.9	be	
	53	352.0	ba	
	54	512.8	?	
C 119.16	5	~~447.9~~ 415.9	eg, fg, gf, cg, dg	
	6	~~447.9~~ 415.9	eg, fg, gf, cg, dg	
	55	512.0	bc	
	56	~~426.9~~ 426	ch, dh	
D 112.15	7	~~386.0~~ 442	eg, fg, gf, cg, dg	
	8	402.0	GA, CB, DB	
	57	469.9	5/1 ci, di	
	58	445.9	9/1 ad, cc	
E 168.28	9	514.9	cd, dd	
	10	500.9	ad, ce, de	
	59	456.9	ga, cb, db	
	60	490.9	gb	
F 111.18	11	473.9	2/1 eb, fb, ac, bc, gg	
	12	479.9	ef, ff,	
	61	4329	gb	
	62	614.7	he	

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amine	sample	mass		structure
G	13	592.8		cg, fg
	14	596.8		ee, fe
	63	574.8	ok	aj
190.27	64	573.8		gb
h	15	540.9 494.9	"	cj, dj
	16	497.9		ah
	65	452.8		bf
142.20	66	540.9		cj, dj
i	17	582.7 / 584.7	?	cf, df
	18	287.0/484.7	mess	
	67	~~282.0/484.7~~ 576.7		ga, cb, db
286.71	68	674.7		be
j	19	640.8	??	cj, dj
	20	638.7		cj, dj
	69		mess	
240.72	70	528.8		ga, cb, db
k	21	563.8		ad, ce, de
	22	429.8 512.8	?	
	71	651.8		cd, fd
231.77	72	677.8, 591.8		ee, fe
l	23	497.8, 407.8		af
	24	617.8	?	
	73	585.8, 539.8		ef, ff
217.87	74	? 583.7		ge
m	25	419.9?		
	26	545.8		cj, dj
	75	590.8		fh
221.01 / 147	76	465.8		ge

Amine	sample	mass	structure
N	27	540.8	aj
	28	655.7	hc
108.14	77	506.8	cj, dj
	78	578.8 573	bf
	29	294.0 383	ab
O	30	? 318 351.9 ?	
109.13	79	? 521.8, 557.8	ec, fc
	80	793.9, 499.8, 431.8	gi
	31	603.9, 621.9 ///	bj
P	32	633.8 ///	? eh, fh
207.27	81	565.8 low ?	
	82	aw	
	33	626.8, 644.7	gh
Q	34	684.7	eh, fh
	83	523.8	bf
211.27	84	585.8	bg
	35	413.9	ga, cb, db
R	36	373.9	? cf, df
	85	467.8	gi
135.15	86	411.9	gd, ce, de
	37	397.7 640.7 wc	?
S	38	276.0	
253.08	87	? 243.1, 401.9	
	88	243.1	
	39	513.9	cf, df
T	40	617.8	cj, dj
	89	533.8	ag
271.30	90	629.8	gc

amino	#	mass		code
U	41	423.9		bf
	42	427.9	10/1	ag
	91	445.8		ad, ce, de
11320	92	511.9	11/1	cj, dj
V	43	572	?	ea fa, gf, cg dg
	44	560.8	?	gj
	93	391.0	?	
18218	94	428.9		cc, dc
W	45	417.9	3/1	ai
	46	507.8		gj
	95	500.8	?	
7511	96	473.9		cj, dj
X	47	530.8		bf
	48	626.8		ee, fe
	97	(565558)		
27067	98	514.8		cf, df
Y	49	412.9	6/1	ai
	50	469.8		cj, dj
	99	370.0 762		cf, df
71	100	381.9	6/1	bf
	101	? 209.2, 580.8		
	102	442.9	3/1	
	103	297.0, 256/, 712.2		
	104	173.3, 243.1		
	105	243.1		
	106	195.2		
	107	392.8	?	
	108	243.1		

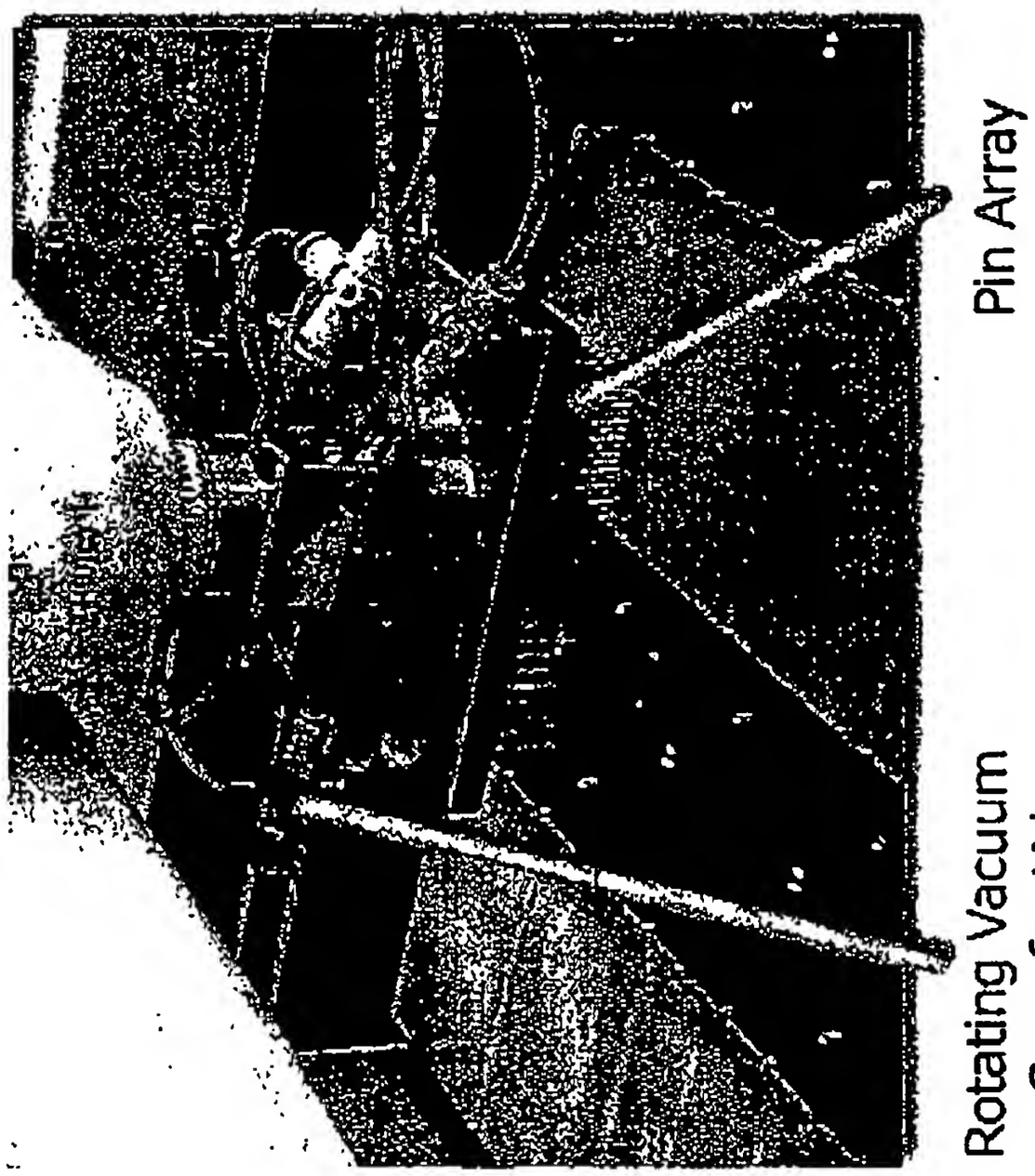

FIGURE 23

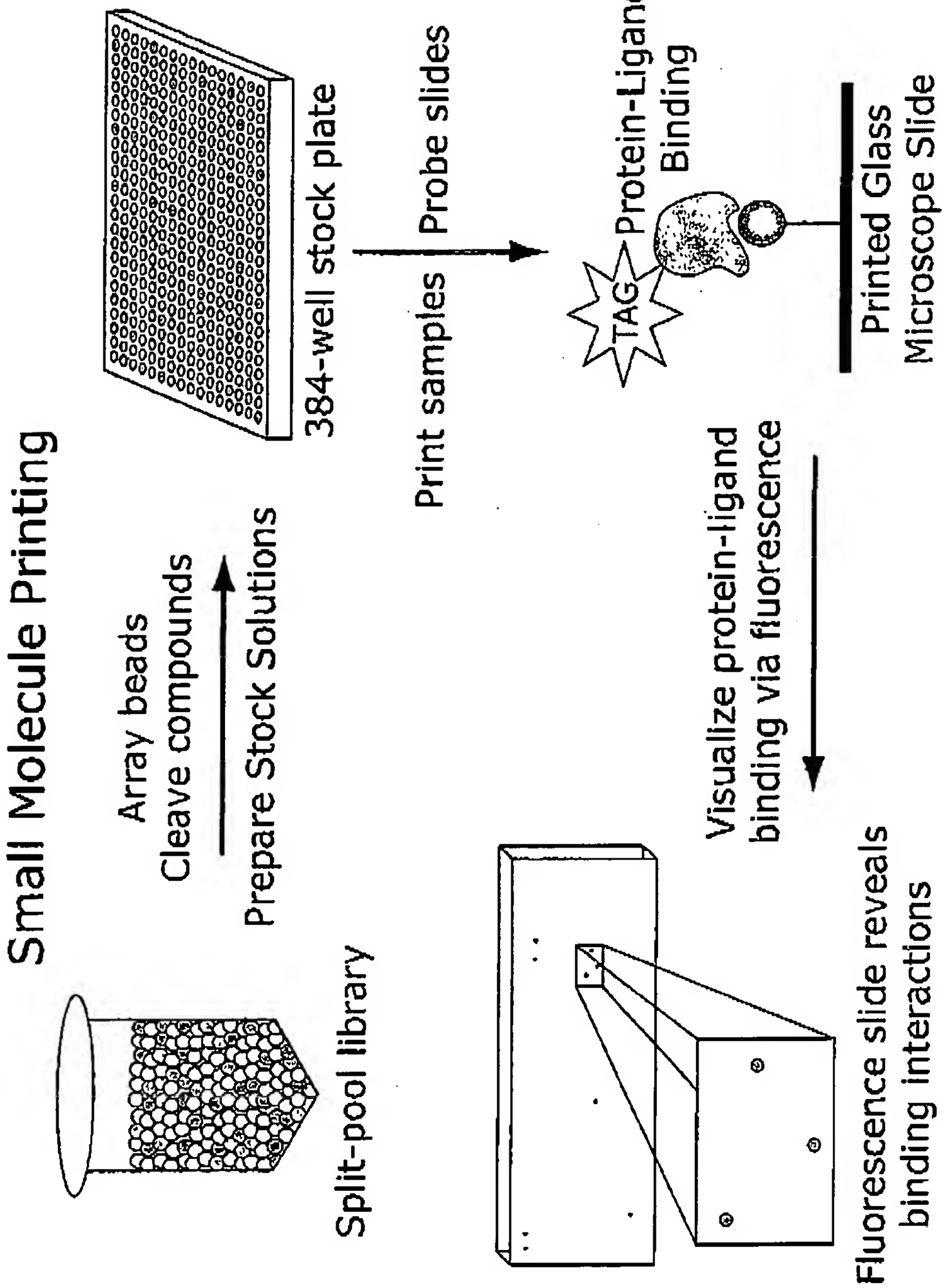

FIGURE 24

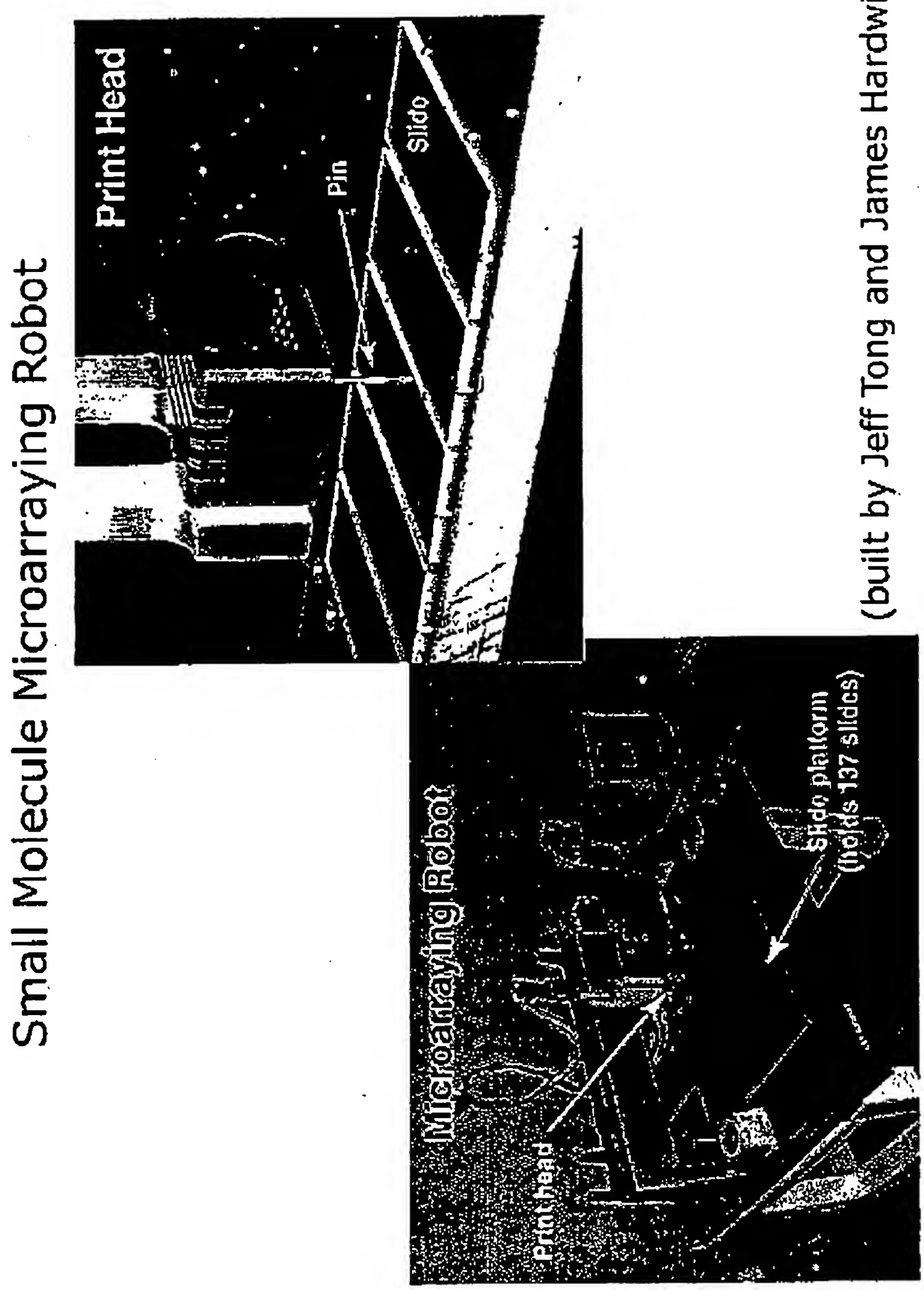

FIGURE 25